

# PATENT SPECIFICATION

(11) 1 468 012

1 468 012

(21) Application No. 37699/73 (22) Filed 9 Aug. 1973  
 (23) Complete Specification filed 9 July 1974  
 (44) Complete Specification published 23 March 1977  
 (51) INT CL<sup>2</sup> C07D 333/38 A61K 31/38  
 (52) Index at acceptance

C2C 1510 200 215 220 226 227 22Y 254 25Y 280 281 282  
 305 311 313 31Y 321 326 32Y 338 342 34Y 366 367  
 368 490 573 574 579 57Y 620 628 62X 65X 670  
 678 697 699 790 79Y KJ KV KZ LS

(72) Inventor ALEXANDER CROSSAN GOUDIE

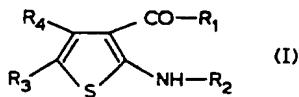


## (54) 2-AMINO-3-CARBOXY-THIOPHENE DERIVATIVES

(71) We, BEECHAM GROUP LIMITED, a British Company of Beecham House, Great West Road, Brentford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to derivatives of 2 - amino - 3 - carboxythiophene, to a process for their manufacture and to pharmaceutical compositions containing them which are useful in the treatment of inflammatory conditions such as arthritis.

The present invention provides compounds of the general formula (I):



wherein  $R_1$  is  $\text{NHR}_5$  or  $\text{OR}_5$ , where  $R_5$  is a hydrogen atom or a lower alkyl group;  $R_2$  is a hydrogen atom or a  $\text{CO}-R_6$  group where  $R_6$  is a lower alkyl group; one of the groups  $R_3$  or  $R_4$  is a substituted phenyl group and the other group  $R_3$  or  $R_4$  is a hydrogen atom or a lower alkyl or optionally substituted phenyl group; and salts thereof if  $\text{COR}_1$  is an acid group.

When used herein, the term "lower alkyl" means an alkyl group of 1-6 carbon atoms. When used herein, the term "substituted phenyl" means the phenyl group substituted by a halogen atom or methyl, trifluoromethyl or methoxy group.

Preferably  $R_2$  is a hydrogen atom. Suitable groups  $R_5$  include the hydrogen atom and the methyl, ethyl, n-propyl, isopropyl, butyl, pentyl and hexyl groups.

Preferred groups  $R_5$  include the hydrogen atom and the methyl and ethyl groups.

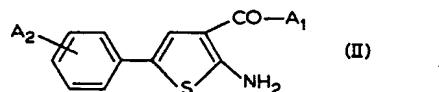
Suitable groups  $R_6$  include the methyl, ethyl and propyl groups.

The preferred groups  $R_6$  are the methyl and ethyl groups.

Preferred groups  $R_6$  include the hydrogen

atom and the methyl, ethyl and phenyl groups, the hydrogen atom being particularly preferred.

One particular suitable sub-group of compounds within formula (I) are those of general formula (II):



wherein  $A_1$  is a group of the formula  $\text{OA}_3$  or  $\text{NHA}_3$ , where  $A_3$  is a hydrogen atom or a lower alkyl group; and  $A_2$  is a halogen atom or a methyl, trifluoromethyl or methoxy group.

Most suitably  $A_1$  is a fluorine, chlorine or bromine atom or a trifluoromethyl group.

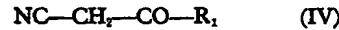
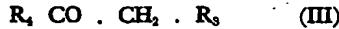
Preferably  $A_1$  is a 4-fluorine atom.

Most suitably  $A_1$  is an amino, methylamino, methoxy or ethoxy group.

Preferably  $A_1$  is an amino group.

When the compound of the formula (I) is a carboxylic acid it may be in the form of an alkali metal salt, alkaline earth metal salt, ammonium or substituted ammonium salt or other conventional salt. Preferred salts include the sodium and potassium salts.

The compounds of formula (I) wherein  $R_2$  is a hydrogen atom may be prepared by the reaction of sulphur and compounds of the general formulae (III) and (IV):



wherein  $R_1$ ,  $R_3$  and  $R_4$  are as defined in relation to formula (I). The compounds wherein  $R_1$  is  $\text{OH}$  are more suitably prepared by the hydrolysis of a corresponding amide or ester.

This condensation reaction is similar to that described by K. Gewald, E. Schinke and H. Boetteher in *Chem. Ber.*, 99, 94-100 (1966).

Normally the reaction is carried out in an

45

55

60

65

70

75

80

5	organic solvent such as dimethylformamide or similar inert solvent at non-extreme temperatures. Generally, the reaction temperatures are ambient or slightly elevated, for example, 15—100°C, preferably 30—80°C.	3 - thiophene carboxamide, m.p. 228—30° (ethanol). 2 - Amino - 5 - (4 - chlorophenyl) - 3 - thiophene carboxamide, m.p. 255—7° (ethanol).	65
10	The condensation reaction is normally carried out in the presence of a base, such as diethylamine, morpholine or triethylamine.	2 - Amino - 5 - (3 - chlorophenyl) - 3 - thiophene carboxamide, m.p. 190—2° (ethanol).	70
15	Compounds of the formula (I) wherein R <sub>2</sub> is a COR <sub>6</sub> group may be prepared from the corresponding amino compound by conventional methods of acylation such as by reaction with an acid anhydride, or more suitably an acid halide, using for example, pyridine as a solvent.	Example 2: 2 - Acetamido - 5 - (4 - fluorophenyl) - 3 - thiophenecarboxamide.	75
20	The compounds of this invention possess useful anti-inflammatory activity. Accordingly, in a further aspect, the invention provides a pharmaceutical composition comprising a compound of the formula (I) as hereinbefore defined, together with a pharmaceutically acceptable carrier. Most suitably the compound of formula (I) included in the composition is one of formula (II) as hereinbefore defined.	A vigorously stirred mixture of 2 - amino - 5 - (4 - fluorophenyl) - 3 - thiophenecarboxamide (0.01 mole) and pyridine (20 ml) at 0° was treated dropwise with acetyl chloride (0.01 mole). The resulting solution was stirred a further 30 minutes at 0° and then poured on to cold water. The precipitate was collected by filtration, washed with water and dried. Recrystallisation from ethanol yielded 2 - acetamido - 5 - (4 - fluorophenyl) - 3 - thiophenecarboxamide (90% by weight, m.p. 230—3°).	80
25	The compositions of this invention may be in the form of conventional oral or parenteral unit dosage forms such as, for example, tablets, capsules, sachets, suppositories, and injectables. For convenience in administration oral forms such as tablets and capsules are preferred. Unit dose forms will normally contain from 6—600 mgs. of active compound, preferably 10—300 mgs, for example, 20—200 mgs.	Example 3. 2 - Amino - 5 - (4 - fluorophenyl) - 3 - thiophene N - methylcarboxamide	85
30	The following examples illustrate the invention.	As example 1, except that N - methylcyanoacetamide replaced cyanoacetamide. The precipitate was recrystallised from aqueous ethanol to afford 2 - amino - 5 - (4 - fluorophenyl) - 3 - thiophene N - methyl carboxamide in 40% by weight yield, m.p. 168° decomp.	90
35	Example 1: 2 - Amino - 5 - (4 - fluorophenyl) - 3 - thiophene carboxamide	Example 4: Ethyl 2 - amino - 5 - (4 - fluorophenyl) - 3 - thiophene carboxylate	95
40	To a stirred mixture of cyanoacetamide (0.1 mole), sulphur (0.1 mole) and diethylformamide (20 ml) at 40—45° was added triethylamine (7.5 ml). The resulting dark brown solution was treated dropwise over 1½ hours, with 4 - fluorophenyl - acetaldehyde (0.1 mole) while the reaction mixture was maintained at 40—45°. After the solution had been stirred at room temperature for 16 hours, it was cooled (ice bath) and poured on to water (60 ml) at 5°C. The precipitate was collected by filtration, washed with water and dried. Recrystallisation from propanol yielded 2 - amino - 5 - (4 - fluorophenyl) - 3 - thiophenecarboxamide (40% by weight, m.p. 227—30°).	As example 1, except that ethyl cyanoacetate replaced cyanoacetamide. Recrystallisation of the crude product from hexane afforded ethyl 2 - amino - 5 - (4 - fluorophenyl) - 3 - thiophene carboxylate, m.p. 98—9°.	100
45	The following compounds were prepared in a similar manner to Example 1 and had the following melting points:	In a similar manner was prepared ethyl 2 - amino - 5 - (3 - chlorophenyl) - 3 - thiophene carboxylate, m.p. 110—11° hexane).	105
50	2 - Amino - 5 - (2 - fluorophenyl) - 3 - thiophene carboxamide, m.p. 170—1° (aqueous ethanol).	Example 5: 2 - Amino - 5 - (4 - fluorophenyl) - 3 - thiophene carboxylic acid.	110
55	2 - Amino - 5 - (4 - methylphenyl) -	A mixture of ethyl 2 - amino - 5 - (4 - fluorophenyl) - 3 - thiophene carboxylate (2g), sodium hydroxide (1g) and ethanol (20 ml) was refluxed for 5 hours, cooled and then concentrated. The solid residue was dissolved in water, filtered and acidified at 0°C. The light brown precipitate was collected by filtration to give pure 2 - amino - 5 - (4 - fluorophenyl) - 3 - thiophene carboxylic acid, m.p. 172—4°.	115
60	2 - Amino - 5 - (4 - chlorophenyl) - 3 - thiophene carboxamide.	Example 6. 2 - Amino - 4 - (4 - chlorophenyl) - 3 - thiophene carboxamide.	120

A mixture of 4 - chloroacetophenone (100 125

g), cyanoacetamide (54.5 g), ammonium acetate (10 g), glacial acetic acid (32 g) and benzene (130 ml) was refluxed overnight with constant removal of water.

5 From the cooled solution was obtained pure (1 - (4 - chlorophenyl) - ethyldene cyanocetamide, m.p. 165-7°.

10 A mixture of 1 - (4 - chlorophenyl) - ethyldene cyanocetamide (37.4 g), sulphur (5.43g), diethylamine (17 ml) and ethanol (70 ml) was stirred at 50-60° for 3 hours, cooled and added to water (200 ml). Recrystallisation of the crude product from benzene gave pure 2 - amino - 4 - (4 - chlorophenyl) - 3 - thiophene carboxamide, m.p. 159-60°.

15 In a similar manner was prepared 2 - amino - 4 - (4 - fluorophenyl) - 3 - thiophene carboxamide, m.p. 150-1° (ethyl acetate/hexane).

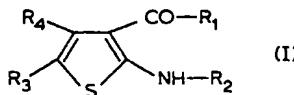
## Example 7.

2 - Amino - 5 - (4 - fluorophenyl) - 4 - phenyl - 3 - thiophene carboxamide.

25 A mixture of 4 - fluorobenzyl phenyl ketone (50 g), morpholine (45 g) and benzene (100 ml) was refluxed overnight with molecular sieve, type 4A, to afford 2 - (4 - fluorophenyl) - 1 - phenyl - 1 - morpholinoethylene. The latter compound (0.2 mole), cyanoacetamide (0.2 mole), diethylamine (2 ml), sulphur (0.2 mole) and ethanol (100 ml) were stirred overnight at room temperature and then added to water. The crude product was recrystallised from ethanol and then from nitromethane to give pure 2 - amino - 5 - (4 - fluorophenyl) - 4 - phenyl - 3 - thiophene carboxamide, m.p. 205-7°.

## WHAT WE CLAIM IS:—

1. A compound of the general formula (I):



wherein R<sub>1</sub> is NHR<sub>3</sub> or OR<sub>3</sub> where R<sub>3</sub> is a hydrogen atom or alkyl group of 1-6 carbon atoms; R<sub>2</sub> is a hydrogen atom or a CO . R<sub>3</sub> group where R<sub>3</sub> is an alkyl group of 1-6 carbon atoms; one of R<sub>3</sub> or R<sub>4</sub> is a phenyl group substituted by a halogen atom or methyl, trifluoromethyl or methoxy group; and the other of R<sub>3</sub> and R<sub>4</sub> is a hydrogen atom or an alkyl group of 1-6 carbon atoms or a phenyl group optionally substituted by a halogen atom or methyl, tri-

fluoromethyl or methoxy group; and salts thereof when COR<sub>1</sub> is an acid group.

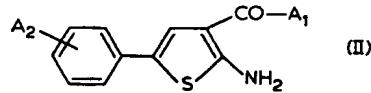
2. A compound as in Claim 1 wherein R<sub>4</sub> is a hydrogen atom or a methyl, ethyl or phenyl group.

3. A compound as in Claim 1 or 2 wherein R<sub>3</sub> is a hydrogen atom or a methyl or ethyl group.

4. A compound as in Claims 1-3 wherein R<sub>2</sub> is a hydrogen atom.

5. A compound as in Claims 1-4 wherein R<sub>4</sub> is a hydrogen atom.

6. A compound of the general formula (II):



wherein A<sub>1</sub> is OA<sub>3</sub> or NHA<sub>3</sub> where A<sub>3</sub> is a hydrogen atom or a lower alkyl group and A<sub>2</sub> is a halogen atom or a methyl, trifluoromethyl or methoxyl group.

7. A compound as in Claim 6 wherein A<sub>2</sub> is a fluorine, chlorine or bromine atom or a trifluoromethyl group.

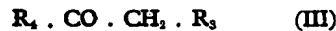
8. A compound as in Claim 7 wherein A<sub>2</sub> is a 4-fluorine atom.

9. A compound as in Claims 6-8 wherein A<sub>1</sub> is a methylamino, methoxy or ethoxy group.

10. A compound as in Claims 6-8 wherein A<sub>1</sub> is an amino group.

11. 2 - Amino - 5 - (4 - fluorophenyl) - 3 - thiophene carboxamide.

12. A process for preparing a compound according to Claim 1 wherein R<sub>2</sub> is a hydrogen atom which comprises the reaction of sulphur and compounds of the general formulae (III) and (IV):



13. A process for preparing a compound according to Claim 1 wherein R<sub>2</sub> is CO . R<sub>3</sub> which comprises acylating a compound according to Claim 1 wherein R<sub>3</sub> is a hydrogen.

14. A pharmaceutical composition which comprises a compound of the formula (I) as defined in Claim 1 together with a pharmaceutically acceptable carrier.

15. A compound according to Claim 1 as in any of the Examples herein.

A. W. WHITE,  
Chartered Patent Agent,  
Agent for the Applicants.

THIS PAGE BLANK (USPTO)